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DT09 Rec'd PCT/PTO 08 SEP 2004

**APPENDIX B**

**Article 34 Amendment**  
**Filed December 15, 2003**

ATTORNEY DOCKET NUMBER: 2003946-0018 (ANDI/PCT)

DT09 Rec'd PCT/PTO 08 SEP 2004

**IN THE EUROPEAN PATENT OFFICE**  
**AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

Applicant: Eisai Co. Ltd.  
Intl. Appln. No.: PCT/US03/07377  
Intl. Filing Date: 7 March 2003  
Priority: U.S.S.N. 60/362,883 filed 8 March 2002  
U.S.S.N. 60/380,711 filed 14 May 2002

For: MACROCYCLIC COMPOUNDS USEFUL AS  
PHARMACEUTICALS

VIA FACSIMILE  
011-49-89-2399-4465  
CONFIRMATION BY  
INTERNATIONAL COURIER

EUROPEAN PATENT OFFICE  
D-80298 MUNICH  
GERMANY  
Authorized Officer: Examiner

Dear Sir/Madam:

**REQUEST FOR AMENDMENT UNDER PCT ARTICLE 34**

1. Applicant respectfully requests authorization from the International Preliminary Examining Authority for amendment under PCT Article 34 and respectfully submits that the replacement sheets, as submitted herewith, reflect claim amendments which do not introduce new matter. Applicant submits herewith replacement sheets number 378-379, 379a, 389-390, 390a, 404-405, 405a and 416-418, to replace sheets number 378-379, 389-390, 404-405 and 416-418, originally filed for this application.

2. In respect of each claim appearing in the international application based on replacement sheets 378-379, 379a, 389-390, 390a, 404-405, 405a and 416-418 submitted herewith, and in accordance with PCT Section 205(b), the following claim(s) is/are:

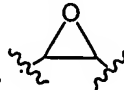
- (i) Unchanged: Claims 2, 36, 119-122 and 124 are unchanged;
- (ii) Replaced: Claims 1, 37, 84 and 123 are replaced with new claims 1, 37, 84 and 123, respectively;

A marked-up copy of Claim Replacements highlighting the changes is provided herewith as attached Appendix A. Deletions are represented in strikethrough, and additions are represented in underlining.

Applicant respectfully submits that no new matter is presented with these amendments. Specifically, claims 1 and 37, as amended, include the proviso that “when *n* is 1; *X* is O; *R*<sub>1</sub> is methyl; *R*<sub>2</sub>, *R*<sub>3</sub>, *R*<sub>7</sub> and *R*<sub>11</sub> are each hydrogen; *R*<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl or –C(=O)C<sub>1-4</sub>alkyl; *R*<sub>6</sub> is hydrogen, OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and *R*<sub>9</sub> is OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; then one or more if the following groups do not occur simultaneously as defined:

(i) *R*<sub>4</sub> is hydrogen; *R*<sub>10</sub> and *R*<sub>8</sub> are independently OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is –CH<sub>2</sub>CH<sub>2</sub>– or –CH=CH–;

(ii) *R*<sub>4</sub> and *R*<sub>8</sub> are each hydrogen; *R*<sub>10</sub> is OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl;


and Y-Z is –CHR<sup>Y</sup>CHR<sup>Z</sup>–, –CH=CH– or ; wherein R<sup>Y</sup> and R<sup>Z</sup> are independently hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkanoyl; and

(iii) *R*<sub>4</sub> and *R*<sub>10</sub> are each hydrogen, OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; *R*<sub>8</sub> is hydrogen, OH, halogen, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is –CH<sub>2</sub>CH<sub>2</sub>–, –CH=CH– or –C(=O)CH<sub>2</sub>–.” which specifically excludes macrocyclic compounds generically and/or specifically disclosed in references 1-6, and pharmaceutical compositions thereof.

Claim 84, as amended, includes the proviso that “when *n* is 1; *X* is O; *R*<sub>1</sub> is methyl; *R*<sub>2</sub>, *R*<sub>3</sub>, *R*<sub>7</sub> and *R*<sub>11</sub> are each hydrogen; *R*<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl or –C(=O)C<sub>1-4</sub>alkyl; *R*<sub>6</sub> is hydrogen, OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and *R*<sub>9</sub> is OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; then one or more if the following groups do not occur simultaneously as defined:

(i) *R*<sub>4</sub> is hydrogen; *R*<sub>10</sub> and *R*<sub>8</sub> are independently OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is –CH<sub>2</sub>CH<sub>2</sub>– or –CH=CH–; and

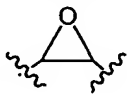
(ii) *R*<sub>4</sub> and *R*<sub>8</sub> are each hydrogen; *R*<sub>10</sub> is OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl;

and Y-Z is –CHR<sup>Y</sup>CHR<sup>Z</sup>–, –CH=CH– or ; wherein R<sup>Y</sup> and R<sup>Z</sup> are independently hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkanoyl; and

(iii) *R*<sub>4</sub> and *R*<sub>10</sub> are each hydrogen, OH, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; *R*<sub>8</sub> is hydrogen, OH, halogen, C<sub>1-4</sub>alkoxy or –OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is –CH<sub>2</sub>CH<sub>2</sub>–, –CH=CH– or –C(=O)CH<sub>2</sub>–; whereby the compound induces mRNA degradation and the method is for treating a disorder resulting from cell proliferation”, which specifically excludes methods disclosed in references 1, 2 and 3.

Claim 123, as amended, includes the proviso that “the following groups do not occur simultaneously as defined: *n* is 1; *X* is O; *R*<sub>1</sub> is methyl; *R*<sub>2</sub>, *R*<sub>3</sub>, *R*<sub>4</sub>, *R*<sub>7</sub>, *R*<sub>8</sub> and *R*<sub>11</sub> are each

hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_9$  and  $R_{10}$  are independently OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-

Z is  $-CHR^YCHR^Z-$ ,  $-CH=CH-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl, which specifically excludes methods for treating restenosis disclosed in reference 2.

Applicant submits that the amendments to the claims, as described above and detailed herein, do not present new matter. Thus Applicant respectfully requests entry of these amendments, and consideration of these amendments in processing the application.

3. The deletion of any claims and any other loss of claimed subject matter is being made solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. Applicant is submitting the present amendments without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant additionally reserves the right to reintroduce the subject matter of any of the canceled claims, or subject matter which might be lost by virtue of amendments set forth in this paper, in the application.

Applicant hereby requests that the ISA begin its examination upon this submission. Favorable action is respectfully requested.

Respectfully submitted,  
CHOATE, HALL & STEWART



Nadège M. Lagneau, Ph.D.  
Agent for Applicant

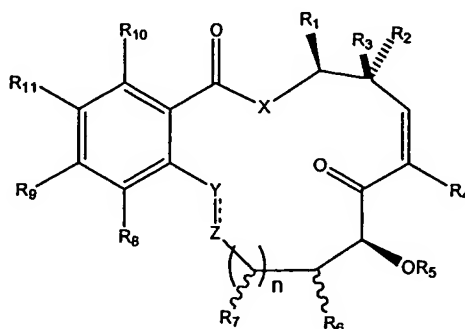
Dated 15 December 2003

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- APPENDIX A -

VERSION WITH MARKINGS TO SHOW CHANGES MADE  
CLAIM REPLACEMENTS

1. A compound having the structure:



(I)

wherein R<sub>1</sub> is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R<sub>1</sub> and R<sub>2</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> is hydrogen, an oxygen protecting group or a prodrug;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting

group, or R<sub>12</sub> and R<sub>13</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R<sub>12</sub> and R<sub>13</sub> are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X<sub>1</sub> and X<sub>2</sub> are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X<sub>2</sub>-R<sub>14</sub> together are N<sub>3</sub> or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R<sub>14</sub> is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is - (C=O)NHR<sub>15</sub> -(C=O)OR<sub>15</sub>, or -(C=O)R<sub>15</sub>, wherein each occurrence of R<sub>15</sub> is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or R<sub>14</sub> is -SO<sub>2</sub>(R<sub>16</sub>), wherein R<sub>16</sub> is an aliphatic moiety, wherein one or more of R<sub>14</sub>, R<sub>15</sub>, or R<sub>16</sub> are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R<sub>8</sub> and R<sub>9</sub> may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R<sub>10</sub> is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

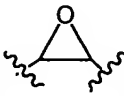
R<sub>11</sub> is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl, CH<sub>2</sub> or S;

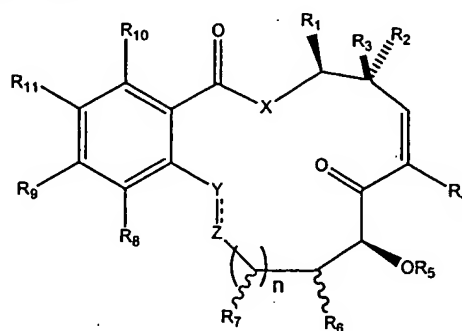
Y is CHR<sub>17</sub>, O, C=O, CR<sub>17</sub> or NR<sub>17</sub>; and Z is CHR<sub>18</sub>, O, C=O, CR<sub>18</sub> or NR<sub>18</sub>, wherein each occurrence of R<sub>17</sub> and R<sub>18</sub> is independently hydrogen or aliphatic, or R<sub>17</sub> and R<sub>18</sub> taken together is -O-, -CH<sub>2</sub>- or -NR<sub>19</sub>-, wherein R<sub>19</sub> is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; and

pharmaceutically acceptable derivatives thereof; ~~thereof~~;

with the proviso that when n is 1; X is O; R<sub>1</sub> is methyl; R<sub>2</sub>, R<sub>3</sub>, R<sub>7</sub> and R<sub>11</sub> are each hydrogen; R<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl or -C(=O)C<sub>1-4</sub>alkyl; R<sub>6</sub> is hydrogen, OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and R<sub>9</sub> is OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $R_4$  is hydrogen;  $R_{10}$  and  $R_8$  are independently OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$  or  $-CH=CH-$ ;
- (ii)  $R_4$  and  $R_8$  are each hydrogen;  $R_{10}$  is OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  
and Y-Z is  $-CHR^YCHR^Z-$ ,  $-CH=CH-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl; and
- (iii)  $R_4$  and  $R_{10}$  are each hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_8$  is hydrogen, OH, halogen,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$ ,  $-CH=CH-$  or  $-C(=O)CH_2-$ .

37. A pharmaceutical composition comprising:  
 a compound having the structure:



(I)

wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;  
R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or R<sub>12</sub> and R<sub>13</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R<sub>12</sub> and R<sub>13</sub> are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X<sub>1</sub> and X<sub>2</sub> are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X<sub>2</sub>-R<sub>14</sub> together are N<sub>3</sub> or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R<sub>14</sub> is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is - (C=O)NHR<sub>15</sub> - (C=O)OR<sub>15</sub>, or - (C=O)R<sub>15</sub>, wherein each occurrence of R<sub>15</sub> is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or R<sub>14</sub> is -SO<sub>2</sub>(R<sub>16</sub>), wherein R<sub>16</sub> is an aliphatic moiety, wherein one or more of R<sub>14</sub>, R<sub>15</sub>, or R<sub>16</sub> are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R<sub>8</sub> and R<sub>9</sub> may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R<sub>10</sub> is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R<sub>11</sub> is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl, CH<sub>2</sub> or S;

Y is CHR<sub>17</sub>, O, C=O, CR<sub>17</sub> or NR<sub>17</sub>; and Z is CHR<sub>18</sub>, O, C=O, CR<sub>18</sub> or NR<sub>18</sub>, wherein each occurrence of R<sub>17</sub> and R<sub>18</sub> is independently hydrogen or aliphatic, or R<sub>17</sub> and R<sub>18</sub> taken




together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and

a pharmaceutically acceptable ~~carrier~~ carrier;

with the proviso that when n is 1; X is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and  $R_9$  is OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; then one or more if the following groups do not occur simultaneously as defined:

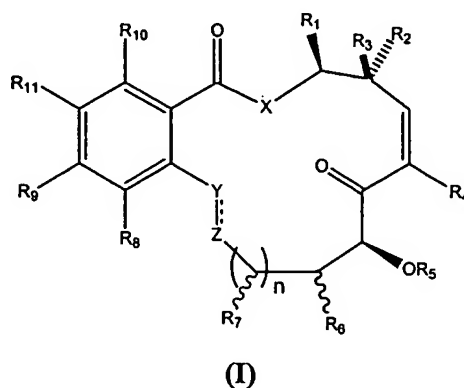
- (i)  $R_4$  is hydrogen;  $R_{10}$  and  $R_8$  are independently OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$  or  $-CH=CH-$ ;
- (ii)  $R_4$  and  $R_8$  are each hydrogen;  $R_{10}$  is OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and

Y-Z is  $-CHR^YCHR^Z-$ ,  $-CH=CH-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkanoyl; and

- (iii)  $R_4$  and  $R_{10}$  are each hydrogen, OH,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl;  $R_8$  is hydrogen, OH, halogen,  $C_{1-4}$ alkoxy or  $-OC(=O)C_{1-4}$ alkyl; and Y-Z is  $-CH_2CH_2-$ ,  $-CH=CH-$  or  $-C(=O)CH_2-$ .

84. A method for treating an inflammatory and/or autoimmune disorder or a disorder resulting from increased angiogenesis and/or cell proliferation comprising:

administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ , -  $X_1(CH_2)_pX_2-R_{14}$ , or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or - $X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is -  $(C=O)NHR_{15}$  -  $(C=O)OR_{15}$ , or -  $(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is - $SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or

more of R<sub>14</sub>, R<sub>15</sub>, or R<sub>16</sub> are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R<sub>8</sub> and R<sub>9</sub> may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R<sub>10</sub> is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R<sub>11</sub> is hydrogen, hydroxyl or protected hydroxyl;


X is absent or is O, NH, N-alkyl, CH<sub>2</sub> or S;

Y is CHR<sub>17</sub>, O, C=O, CR<sub>17</sub> or NR<sub>17</sub>; and Z is CHR<sub>18</sub>, O, C=O, CR<sub>18</sub> or NR<sub>18</sub>, wherein each occurrence of R<sub>17</sub> and R<sub>18</sub> is independently hydrogen or aliphatic, or R<sub>17</sub> and R<sub>18</sub> taken together is -O-, -CH<sub>2</sub>- or -NR<sub>19</sub>-, wherein R<sub>19</sub> is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and

a pharmaceutically acceptable carrier or ~~diluent~~ diluent;

with the proviso that when n is 1; X is O; R<sub>1</sub> is methyl; R<sub>2</sub>, R<sub>3</sub>, R<sub>7</sub> and R<sub>11</sub> are each hydrogen; R<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl or -C(=O)C<sub>1-4</sub>alkyl; R<sub>6</sub> is hydrogen, OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and R<sub>9</sub> is OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; then one or more if the following groups do not occur simultaneously as defined:

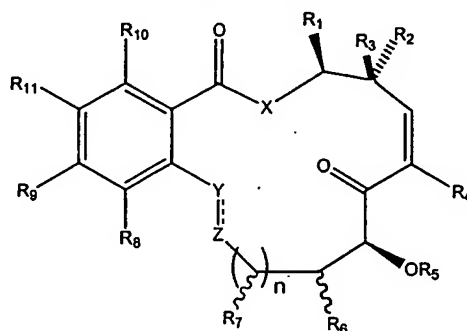
- (i) R<sub>4</sub> is hydrogen; R<sub>10</sub> and R<sub>8</sub> are independently OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is -CH<sub>2</sub>CH<sub>2</sub>- or -CH=CH-; and
- (ii) R<sub>4</sub> and R<sub>8</sub> are each hydrogen; R<sub>10</sub> is OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and

Y-Z is -CHR<sup>Y</sup>CHR<sup>Z</sup>-, -CH=CH- or ; wherein R<sup>Y</sup> and R<sup>Z</sup> are independently hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkanoyl; and

- (iii) R<sub>4</sub> and R<sub>10</sub> are each hydrogen, OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; R<sub>8</sub> is hydrogen, OH, halogen, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is -CH<sub>2</sub>CH<sub>2</sub>-, -CH=CH- or -C(=O)CH<sub>2</sub>-; whereby the compound induces mRNA degradation and the method is for treating a disorder resulting from cell proliferation.

123. A method for preventing or reducing the rate of restenosis, comprising:

inserting a stent into an obstructed blood vessel, the stent having a generally tubular structure, the surface of the structure being coated with (or otherwise adapted to release) a composition comprising a compound having the structure:



(I)

wherein  $R_1$  is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

$R_1$  and  $R_2$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

$R_1$  and  $R_3$ , when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen or a protecting group;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, lower alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or R<sub>12</sub> and R<sub>13</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R<sub>12</sub> and R<sub>13</sub> are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X<sub>1</sub> and X<sub>2</sub> are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X<sub>2</sub>-R<sub>14</sub> together are N<sub>3</sub> or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R<sub>14</sub> is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is -(C=O)NHR<sub>15</sub>-(C=O)OR<sub>15</sub>, or -(C=O)R<sub>15</sub>, wherein each occurrence of R<sub>15</sub> is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or R<sub>14</sub> is -SO<sub>2</sub>(R<sub>16</sub>), wherein R<sub>16</sub> is an alkyl moiety, wherein one or more of R<sub>14</sub>, R<sub>15</sub>, or R<sub>16</sub> are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R<sub>8</sub> and R<sub>9</sub> may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R<sub>10</sub> is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R<sub>11</sub> is hydrogen, hydroxyl or protected hydroxyl;

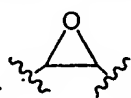
X is absent or is O, NH, N-alkyl, CH<sub>2</sub> or S;

Y is CHR<sub>17</sub>, O, C=O, CR<sub>17</sub> or NR<sub>17</sub>; and Z is CHR<sub>18</sub>, O, C=O, CR<sub>18</sub> or NR<sub>18</sub>, wherein each occurrence of R<sub>17</sub> and R<sub>18</sub> is independently hydrogen or lower alkyl, or R<sub>17</sub> and R<sub>18</sub> taken together is -O-, -CH<sub>2</sub>- or -NR<sub>19</sub>-, wherein R<sub>19</sub> is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and optionally

a pharmaceutically acceptable carrier or diluent;

such that the obstruction is eliminated and the composition is delivered in amounts effective to prevent or reduce the rate of ~~restenosis~~; restenosis;

with the proviso that the following groups do not occur simultaneously as defined: n is 1; X is O; R<sub>1</sub> is methyl; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>11</sub> are each hydrogen; R<sub>5</sub> is hydrogen, C<sub>1-4</sub>alkyl or -C(=O)C<sub>1-4</sub>alkyl; R<sub>6</sub> is hydrogen, OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; R<sub>9</sub> and R<sub>10</sub> are independently OH, C<sub>1-4</sub>alkoxy or -OC(=O)C<sub>1-4</sub>alkyl; and Y-Z is -CHR<sup>Y</sup>CHR<sup>Z</sup>-, -

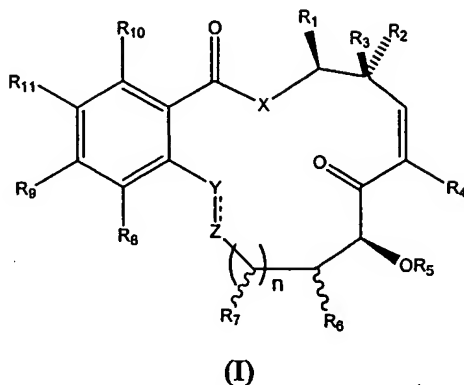
CH=CH- or ; wherein R<sup>Y</sup> and R<sup>Z</sup> are independently hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkanoyl.

**SUBSTITUTE SHEETS**

## CLAIMS

We claim:

1. A compound having the structure:



wherein  $R_1$  is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$R_2$  and  $R_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

$R_1$  and  $R_2$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

$R_1$  and  $R_3$ , when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$R_4$  is hydrogen or halogen;

$R_5$  is hydrogen, an oxygen protecting group or a prodrug;

$R_6$  is hydrogen, hydroxyl, or protected hydroxyl;

$n$  is 0-2;

$R_7$ , for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;



wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$   $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

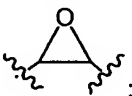
$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or lower alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; and

pharmaceutically acceptable derivatives thereof;

with the proviso that when  $n$  is 1;  $X$  is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_1$ -

alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{R}_9$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $\text{R}_4$  is hydrogen;  $\text{R}_{10}$  and  $\text{R}_8$  are independently  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}=\text{CH}-$ ;
- (ii)  $\text{R}_4$  and  $\text{R}_8$  are each hydrogen;  $\text{R}_{10}$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CHR}^{\text{Y}}\text{CHR}^{\text{Z}}-$ ,  $-\text{CH}=\text{CH}-$  or ;

wherein  $\text{R}^{\text{Y}}$  and  $\text{R}^{\text{Z}}$  are independently hydrogen,  $\text{C}_{1-4}\text{alkyl}$  or  $\text{C}_{1-4}\text{alkanoyl}$ ; and

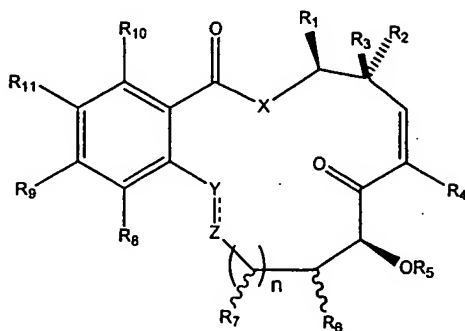
- (iii)  $\text{R}_4$  and  $\text{R}_{10}$  are each hydrogen,  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ;  $\text{R}_8$  is hydrogen,  $\text{OH}$ , halogen,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}(=\text{O})\text{CH}_2-$ .

2. The compound of claim 1, where the following groups do not occur simultaneously as defined:

$\text{X}$  is oxygen,

and pharmaceutically acceptable derivatives thereof.

37. A pharmaceutical composition comprising:  
a compound having the structure:



(I)

wherein R<sub>1</sub> is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R<sub>1</sub> and R<sub>2</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> is hydrogen, an oxygen protecting group or a prodrug;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

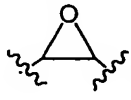
$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or lower alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and

a pharmaceutically acceptable carrier;

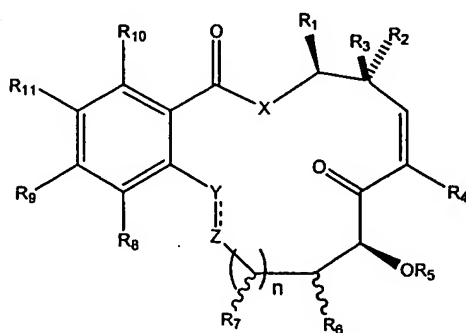
with the proviso that when  $n$  is 1;  $X$  is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_{1-}$

alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{R}_9$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $\text{R}_4$  is hydrogen;  $\text{R}_{10}$  and  $\text{R}_8$  are independently  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}=\text{CH}-$ ;
- (ii)  $\text{R}_4$  and  $\text{R}_8$  are each hydrogen;  $\text{R}_{10}$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CHR}^{\text{Y}}\text{CHR}^{\text{Z}}-$ ,  $-\text{CH}=\text{CH}-$  or ; wherein  $\text{R}^{\text{Y}}$  and  $\text{R}^{\text{Z}}$  are independently hydrogen,  $\text{C}_{1-4}\text{alkyl}$  or  $\text{C}_{1-4}\text{alkanoyl}$ ; and

- (iii)  $\text{R}_4$  and  $\text{R}_{10}$  are each hydrogen,  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ;  $\text{R}_8$  is hydrogen,  $\text{OH}$ , halogen,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}(=\text{O})\text{CH}_2-$ .

84. A method for treating an inflammatory and/or autoimmune disorder or a disorder resulting from increased angiogenesis and/or cell proliferation comprising:  
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



(I)

wherein R<sub>1</sub> is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R<sub>1</sub> and R<sub>2</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> is hydrogen, an oxygen protecting group or a prodrug;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

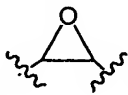
$X$  is absent or is O, NH, N-alkyl,  $CH_2$  or S;

$Y$  is  $CHR_{17}$ , O,  $C=O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ , O,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together is  $-O-$ ,  $-CH_2-$  or  $-NR_{19}-$ , wherein  $R_{19}$  is hydrogen or lower alkyl, and  $Y$  and  $Z$  may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and

a pharmaceutically acceptable carrier or diluent;

with the proviso that when  $n$  is 1;  $X$  is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_7$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $C_{1-4}$ alkyl or  $-C(=O)C_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $C_1$ .

alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{R}_9$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; then one or more if the following groups do not occur simultaneously as defined:

- (i)  $\text{R}_4$  is hydrogen;  $\text{R}_{10}$  and  $\text{R}_8$  are independently  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$  or  $-\text{CH}=\text{CH}-$ ; and
- (ii)  $\text{R}_4$  and  $\text{R}_8$  are each hydrogen;  $\text{R}_{10}$  is  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CHR}^{\text{Y}}\text{CHR}^{\text{Z}}-$ ,  $-\text{CH}=\text{CH}-$  or ; wherein  $\text{R}^{\text{Y}}$  and  $\text{R}^{\text{Z}}$  are independently hydrogen,  $\text{C}_{1-4}\text{alkyl}$  or  $\text{C}_{1-4}\text{alkanoyl}$ ; and

- (iii)  $\text{R}_4$  and  $\text{R}_{10}$  are each hydrogen,  $\text{OH}$ ,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ;  $\text{R}_8$  is hydrogen,  $\text{OH}$ , halogen,  $\text{C}_{1-4}\text{alkoxy}$  or  $-\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$ ; and  $\text{Y-Z}$  is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}(=\text{O})\text{CH}_2-$ ; whereby the compound induces mRNA degradation and the method is for treating a disorder resulting from cell proliferation.



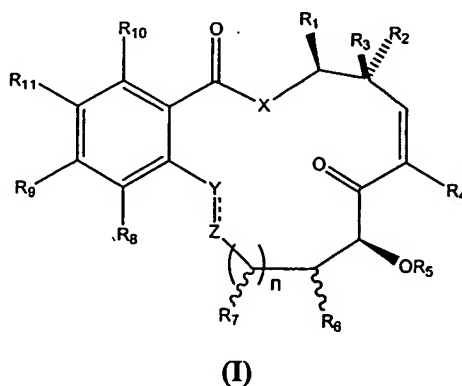
Y is  $\text{CHR}_{17}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{17}$  or  $\text{NR}_{17}$ ; and Z is  $\text{CHR}_{18}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{18}$  or  $\text{NR}_{18}$ , wherein each occurrence of  $\text{R}_{17}$  and  $\text{R}_{18}$  is independently hydrogen or lower alkyl, or  $\text{R}_{17}$  and  $\text{R}_{18}$  taken together is  $-\text{O}-$ ,  $-\text{CH}_2-$  or  $-\text{NR}_{19}-$ , wherein  $\text{R}_{19}$  is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and  
a pharmaceutically acceptable carrier or diluent.

120. The method of claim 119, wherein in the step of administering, the composition is administered topically.

121. The method of claim 119, wherein the photodamage is skin wrinkles.

122. The method of claim 119, wherein the photodamage is a skin cancer.

123. A method for preventing or reducing the rate of restenosis, comprising:  
inserting a stent into an obstructed blood vessel, the stent having a generally tubular structure, the surface of the structure being coated with (or otherwise adapted to release) a composition comprising a compound having the structure:



wherein  $\text{R}_1$  is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

$\text{R}_2$  and  $\text{R}_3$  are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

R<sub>1</sub> and R<sub>2</sub>, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> is hydrogen or a protecting group;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, lower alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or R<sub>12</sub> and R<sub>13</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R<sub>12</sub> and R<sub>13</sub> are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X<sub>1</sub> and X<sub>2</sub> are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X<sub>2</sub>-R<sub>14</sub> together are N<sub>3</sub> or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R<sub>14</sub> is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is - (C=O)NHR<sub>15</sub> - (C=O)OR<sub>15</sub>, or - (C=O)R<sub>15</sub>, wherein each

occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is  $-\text{SO}_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;


X is absent or is O, NH, N-alkyl,  $\text{CH}_2$  or S;

Y is  $\text{CHR}_{17}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{17}$  or  $\text{NR}_{17}$ ; and Z is  $\text{CHR}_{18}$ , O,  $\text{C}=\text{O}$ ,  $\text{CR}_{18}$  or  $\text{NR}_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or lower alkyl, or  $R_{17}$  and  $R_{18}$  taken together is  $-\text{O}-$ ,  $-\text{CH}_2-$  or  $-\text{NR}_{19}-$ , wherein  $R_{19}$  is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; pharmaceutically acceptable derivatives thereof; and optionally

a pharmaceutically acceptable carrier or diluent;

such that the obstruction is eliminated and the composition is delivered in amounts effective to prevent or reduce the rate of restenosis;

with the proviso that the following groups do not occur simultaneously as defined: n is 1; X is O;  $R_1$  is methyl;  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_7$ ,  $R_8$  and  $R_{11}$  are each hydrogen;  $R_5$  is hydrogen,  $\text{C}_{1-4}$ alkyl or  $-\text{C}(=\text{O})\text{C}_{1-4}$ alkyl;  $R_6$  is hydrogen, OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl;  $R_9$  and  $R_{10}$  are independently OH,  $\text{C}_{1-4}$ alkoxy or  $-\text{OC}(=\text{O})\text{C}_{1-4}$ alkyl;

and Y-Z is  $-\text{CHR}^Y\text{CHR}^Z-$ ,  $-\text{CH}=\text{CH}-$  or ; wherein  $R^Y$  and  $R^Z$  are independently hydrogen,  $\text{C}_{1-4}$ alkyl or  $\text{C}_{1-4}$ alkanoyl.

124. A method for expanding the lumen of a body passageway, comprising:

inserting a stent into the passageway, the stent having a generally tubular structure, the surface of the structure being coated with (or otherwise adapted to release) a composition comprising a compound having the structure: